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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/640,887	LEE ET AL.	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15 and 54-58* is/are pending in the application.

4a) Of the above claim(s) *54-58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 October 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This Action is in response to the communication filed on 3/29/04, as a supplement to the Paper filed 2/23/04. The amendment has been entered. Claim 1 has been amended. Claims 16-53 have been cancelled. Claims 54-58 have been withdrawn from consideration for the reasons previously set forth. Claims 1-15 are addressed herein.

2. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Election/Restrictions

3. Applicants submitted claims (54-58) that were withdrawn from consideration in the previous Office Action (9/22/03). The claims were withdrawn from further consideration because claims 54-58 are drawn to a transgenic non-human aquatic organism whose genome comprises an inserted transgene encoding a molecule that interferes with expression of endogenous GDF-8. The elected claims are drawn to an invention that is patentably distinct from the invention of clains 54-58. Therefor, the inventions are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions the different inventions are materially different and have different modes of operation and different functions. For instance, the invention of the newly submitted claims requires expression of transgene molecule that interferes

with expression of endogenous GDF-8, such as an antisense nucleic acid, ribozymes or dominant negative GDF-8 polypeptide. The elected invention requires an insertion into the endogenous GDF-8 gene, which disrupts the expression of GDF-8 (i.e. knockout of GDF-8 gene).

4. Furthermore, because these inventions are distinct for the reasons given above and the search required for each Group is different, restriction for examination purposes as indicated is proper. For instance, the search for the new claims requires searching for aquatic organisms comprising transgenes which when expressed, inhibit the expression of GDF-8; while the search of the elected invention requires searching for transgenic aquatic organisms that have an insertion specifically in the GDF-8 gene such that expression of the GDF-8 gene is disrupted.

Response to Arguments

5. Applicant's arguments filed 2/23/04 have been fully considered but they are not persuasive. Applicants contend that the compositions required to practice claims 54-58 overlap with the compositions required to practice claims 1-15 (see p. 10 of the response). Specifically, applicants argue that the transgene used to make the transgenic organism of claims 1-15 and 54-58 must comprise GDF-8 sequences such as the GDF-8 sequence for targeting insertion, GDF-8 antisense sequence and GDF-8 dominant negative sequence. This is not persuasive as the sequences used in each example of applicants' argument has different function and modes of operation. For instance the GDF-8 sequence of the targeting vector is to target integration into the GDF-8 gene. The GDF-8 antisense sequence inhibits translation of GDF-8. GDF-8 dominant negative sequence encodes a dominant negative inhibitor that is a polypeptide and that inhibits the function of GDF-8 polypeptide. Therefore, the different examples presented do not use the SAME materials (i.e., different material are required) and the alleged common sequences

do not have the same mode of operation/function. Additionally, applicants argue that searching "GDF-8 polynucleotide sequences" and "transgenic aquatic organism" would necessarily reveal art relevant to claims 54-58. This is also not persuasive as the searches required for the new claims are not co-extensive with the search for the elected claims. For example, the search for the new claims would require the search terms: GDF-8 antisense, dominant negative GDF-8 polypeptide, ribozymes and triplex agent. These terms are not required for the search of the elected claims, prima facie evidence of a search burden. Applicants also argue that the pending claims all have a common effect, that effect being decreased GDF-8 activity. However, as indicated above, the materials and method steps used to decrease GDF-8 activity are different and function by different actions (i.e., different modes). Therefore, the claims are patentably distinct and applicants' arguments are not persuasive.

Specification

The objection to the specification is withdrawn in view of the amendment removing the active hyperlinks from the specification.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 2, 4, 5, and 7-14 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record.

Response to Arguments

8. Applicant's arguments filed 2/23/04 have been fully considered but they are not persuasive. Applicants contend that the disclosed piscine and amphibian GDF-8 sequences provide sufficient representative species such that the skilled artisan would have known that Applicants were in possession of GDF-8 sequences of aquatic organisms, including, for example, crustacean, mollusk, chordate, gastropod, pelecypod, cephalopod, echinoderm, piscine and amphibian GDF-8 sequences (see, e.g., claims 2 and 3). More specifically, applicants assert, the specification discloses specific examples of piscine and amphibian GDF-8 sequences, and further discloses that the C-terminal active portion of GDF-8 proteins of organisms as diverse as piscine, amphibian (Xenopus) and human share at least about 88% sequence identity (see, e.g., page 78, lines 19-23; see, also, Figures 19 and 20). In addition, the specification discloses that probes based on the murine GDF-8 sequence were used to identify the disclosed zebrafish and salmon cDNA sequences (see Example 9, pages 77-78); the additionally disclosed fish and amphibian GDF-8 sequence were obtained similarly. Therefore, applicants argue, in view of the numerous exemplified GDF-8 sequences in the subject application, and the disclosure that probes based on a murine GDF-8 sequence allowed the identification of the exemplified piscine and amphibian GDF-8 CDNA sequences, **it submitted that the skilled artisan reasonably would have known that GDF-8 sequences of any other aquatic organisms of interest, including those as recited in the claims, readily could be obtained using the disclosed methods** (emphasis added). As

such, applicants assert, the skilled artisan reasonably would have known that Applicants were in possession of the genus of aquatic organism GDF-8 nucleotide sequences.

These arguments are not persuasive. It is respectfully pointed out that applicants' arguments indicate (i.e., it is admitted) that additional experimentation is required to obtain the GDF-8 sequences of any other aquatic organism. Therefore, in order to make/use the claimed invention the GDF-8 genes of the additional aquatic organisms (i.e. those organisms which the GDF-8 gene has not been disclosed) would have to be first isolated and identified using a disclosed hybridization technique. However, it is respectfully pointed out that, with respect to written description of DNA (e.g., genes), the Federal Circuit has indicated:

> "An adequate written description of DNA... 'requires a precise definition, such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel,* 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Circ. 1993). Accordingly, 'an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. At 1170, 25 USPQ2d at 1606.

Therefore, applicants' argument that one of skill in the art would have recognized that applicants were in possession of the genus of aquatic GDF-8 genes is not persuasive.

9. Additionally, claims 1, 2, 4, 5, and 7-14 also remain rejected under 35 U.S.C. 112, first paragraph, in view of the written description rejection above, as failing to comply with the enablement requirement for the reasons of record. The claim(s) contains subject matter which

was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Response to Arguments

10. Applicant's arguments filed 2/23/04 have been fully considered but they are not persuasive. Applicants argue that the specification discloses probes based on a murine GDF-8 sequence were used to obtain GDF-8 CDNA of zebrafish and salmon, and further discloses that these evolutionarily diverse organisms (i.e., mammals v. fish) express GDF-8 proteins that share 88% identity in the C-terminal portion of the protein. Applicants contend that the skilled artisan reasonably would have expected that GDF-8 nucleotide sequences of other aquatic organisms could be obtained using similar methods and while some experimentation may have been required to obtain GDF-8 sequences of other aquatic organisms, such experimentation would have been routine, using methods well known in the art and, therefore, would not amount to "undue experimentation".

11. In response, it is respectfully pointed out that the claims encompass all "non-human aquatic organisms"—a genus encompassing thousands, possibly millions of different species including species as diverse as marine mammals (such as seals, whales, sea otters, porpoises, manatees, etc.), marine plants (such as sea weeds, etc.), aquatic micro-organisms (such as plankton, bioluminescent organisms, etc.) as well as all other non-human living organisms that live primarily in the water, such as: sharks, starfish, shellfish, crustaceans, sea snails, turtles, seahorses, anemones, coral, etc, as well as all aquatic organisms that have yet to be identified. Therefore, it is clear that genus encompass a vast number of diverse different species, of which there is only the description of certain piscine species and one xenopus species (it is noted that

bovines and mice are not aquatic organisms). Considering the huge breadth of species encompassed by the claims, the identification of the piscine and xenopus GDF-8 genes does not adequately describe a "representative number" of non-human aquatic organisms. Although there may be some sequence homology between the known GDF-8 sequences, there is insufficient evidence to indicate that the sequences of the known GDF-8 genes could be used to "routinely" identify and isolate the GDF-8 genes of a "representative number" of species encompassed by the claims. For instance one of skill in the art would not consider it a matter or routine experimentation to isolate a genes of aquatic microorganisms based on the known sequence of a fish or frog gene. Therefore, in view of the vast breadth of species encompassed by the claims, additional experimentation would have been required to identify the GDF-8 genes of a "representative number" of non-human aquatic organisms, and considering that the species are as diverse as fish, sea weed, micro-organisms, starfish, anemones, etc., the amount of additional experimentation is deemed to be undue.

12. Claim(s) 1-15 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons of record.

Response to Arguments

13. Applicant's arguments filed 2/23/04 have been fully considered but they are not persuasive. Applicants argue that only specific claims (e.g., claim 8) specifically require the use of ES cells. Applicants point out that claim 1, for example, encompasses the use of ES cells in

only one aspect and claim 7 specifically requires the use of cells other than ES cells to make the claimed transgenic aquatic organisms.

14. In reply to this argument, it is respectfully pointed out that if the claim encompasses the use of ES cells, regardless if it is only in one aspect of the claim, the rejection is still appropriate.

15. With respect to the use of non-ES cells to make the transgenic aquatic organisms, applicants argue that the methods of effecting homologous recombination in a cell have long been known and are routine in the art, and that essentially any nucleic acid molecule having the appropriate gene sequences can undergo homologous recombination in a cell. Applicants contend that nucleic acid molecules that are introduced by injection into Xenopus oocytes undergo homologous recombination in the oocytes, and the mechanism appears to be similar to that in other cells, including plant, yeast and mammalian cells. As such, it is asserted, the skilled artisan would have known that homologous recombination can be used to disrupt an endogenous GDF-8 gene, for example, in Xenopus oocytes, and that such oocytes could be used according to a method of the invention to obtain a transgenic aquatic organism (see, e.g., claim 7). Further, Applicants argue, in view the specification, which discloses, for example, that a transgene can be microinjected into embryonal cells from various stages of development, including cells of a zygote, which are the best target for microinjection of the transgene (page 56, lines 13-15), as well as knowledge in the art that homologous recombination can be effected in a wide variety of cells, the skilled artisan would have known that the methods of the invention could be practiced with a variety of cells other than ES cells.

16. In response, although homologous recombination has been known in the art, there are no specific examples in the prior art or in the instant specification which indicates that homologous

recombination can be used in a non-ES cell to make a transgenic (i.e. knock-out) aquatic organism. In order to be perfectly clear, not a single aquatic organism that has been genetically engineered by homologous recombination such that a specific alteration is in a specifically targeted gene any be found in the prior, or post filing art. Nor have applicants submitted any evidence that such an aquatic organism has ever been successfully produced. Furthermore, in order to support the Examiner's position previously set forth that the claimed methods of creating site-directed mutations would not be a matter of routine experimentation, neither at the time of filing nor even presently, the following post-filing references are made of record.

17. First, Lekven (Physiol Genomics 2000) teaches, "Despite all of the strengths mentioned, one technology lacking in the zebrafish system, **indeed in any vertebrate system other than the mouse, is the ability to target mutations to specific genes through homologous recombination.** The utility of this technology is apparent to anyone who has tried to determine a gene's function after cloning based on homology." (See p. 38, first column).

18. Second, Wienholds (Genome Research 2003) teaches, "Attempts to implement a method for generating permanent knockouts similarly (as routinely done for mouse) **have not been successful yet for zebrafish.** Such an approach requires homologous recombination in pluripotent embryonic stem (ES) cells and subsequent generation of chimeric embryos. Although ES-like cells for zebrafish have been described... and the generation of some chimeras have been reported..., no targeted knockouts have been obtained using this approach." (See page 2700, paragraph bridging columns 1 and 2).

19. Therefore, it is clear that it is not a matter of routine experimentation to make a transgenic aquatic organism wherein a specific gene, such as GDF-8, has been disrupted using homologous recombination and ES or non-ES cells.

20. Applicants also assert the following:

"With respect to ES cells of aquatic species, it is submitted that methods for obtaining ES cells of various species are becoming more routine, and that ES cells of new species are continually being described (see, e.g., U.S. Pat. No. 6,103,523, rabbit ES cells; U.S. Pat. No. 6,271,436, porcine ES cells; U.S. Pat. No. 6,200,806, primate ES cells; and U.S. Pat. No. 6,107,543, bovine ES cells). Further, ES cells of aquatic species have been described. For example, Hong et al. describe medaka fish ES cells (Proc. Natl. Acad. Sci., USA 95:3679-3684, 1998; a copy of which is attached as Exhibit B), Bejar et al. describe Sparus aurata ES cells (Transgenic Res. 1 1:279-289, 2002; Abstract attached as Exhibit C), and Chen et al. describe sea bream ES ceils (J. Fish Biol. 63:795, 2043; Abstract attached as Exhibit D). As such, it is submitted that methods for obtaining ES cells are becoming more routine in the art. It is noted that the Office Action cites to Prell et al. with respect to the medaka fish ES cells (citing to Hong et al., 1998, which is the attached Exhibit B). It is alleged in the Office Action that there is no indication that the medaka fish ES cells integrated into the germ line of the fish (O.A., page 12). Applicants point out, however, that Hong et al. do not address this issue (see Exhibit B), but state that the medaka fish ES cells "appear to be a fish equivalent of mouse ES cells" (see page 3681, paragraph bridging columns). As such, it is submitted that, absent objective evidence to

the contrary, the Hong et al. reference should be taken for what it discloses, i.e., that the medakafish ES cells appear to be the equivalent of mouse ES cells."

In response, with respect to the assertion that obtaining ES cells of various species are becoming more routine, it is not relevant that obtaining methods of ES cells are becoming more routine. What is relevant is that the specification at the time of filing must disclose to those of skill in the art how to make the claimed invention. For the reasons indicated previously and herein, it is clear that at the time of filing applicants have not disclosed how to make the claimed invention as totiopotent ES cells were not described, nor is there any evidence in the prior or post filing art that totiopotent ES cells have been isolated for *any* aquatic organism. With respect to applicants assertion that Hong teaches medakafish ES cells that appear to be a fish equivalent of mouse ES cells, it is respectfully pointed out that although Hong does indicate his belief that the medakafish ES cells are equivalent to mouse ES cells, the evidence presented by Hong clearly indicates that the ES cells could only be used to make chimeric fish. There is no indication that the alleged ES cells could be used to make alterations in the germ cells of the fish—an essential requirement for breeding the chimera to homozygosity. Furthermore, there is no examples found in the prior or post filing art that that the alleged medaka fish ES cells could be used to make knockout organisms. With respect to the teaching of Prell that no proven ES cells colonizing the germ line have been established for vertebrate species other than mouse and chicken thus far. It is respectfully pointed out that Prell does contradict the teaching of Hong by specifically indicating, "These [medakafish] ES cells were competent to form chimeras with a high contribution of the transplanted cells to numerous organs..." (See p. 225, first column).

Furthermore, there is no indication that the medaka fish ES cells integrated into the germ line of the fish. It is also respectfully pointed out that the claims are not limited to Medakafish, and encompass all non-human aquatic organisms, and there is no evidence found in the specification or prior art that indicates totiopotent ES cells had been isolated for all of these organisms—an essential element to creating germ-line transgenic organisms.

Applicants also argue that the teachings of Kambadur and Moreadith wherein mutations in the bovine and mouse GDF-8 cells result in the same general phenotype, increased muscle mass, but through different mechanisms. Therefore, applicants assert that the one of skill in the art would expect a GDF-8 disruption to result in increased muscle mass, regardless of the species.

In response, Kambadur and Moreadith were cited in order to point out that a specific gene disruption in one species does not always result in the exact same outcome in a different species. Although the end result, increased muscle mass, was similar in the bovine and mouse models, this result was due, unexpectedly, to completely different mechanisms in the animals. Therefore, it would be unpredictable what effect the disruption of the GDF-8 gene would have in aquatic organisms. It is acknowledged that the GDF-8 mutations in mouse and bovine both resulted in increased muscle mass. However, there is evidence that the expected result does not always appear in different species. With respect to the instant arguments, it is acknowledged that one of skill in the art would expect the increased muscle mass phenotype in any GDF-8 knockout animal. However, for the reasons indicated previously and herein, there is no disclosure in the art or in the specification which would teach one of skill in the art how to make the desired targeted site directed mutation in an aquatic organism.

The submitted exhibits have been fully considered. However the rejections indicated above are not withdrawn for the reasons indicated herein.

Conclusion

No claim is allowed.

This application contains claims 54-58 drawn to an invention nonelected with traverse as previously indicated. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

21. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (571) 272-0756. The examiner can normally be reached on M-F (8:00-5:30) with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Art unit 1635

DAVE T. NGUYEN
PRIMARY EXAMINER